REMARKS

In view of the above amendments and the following remarks, reconsideration of the outstanding office action is respectfully requested. Pursuant to 37 CFR § 1.121, attached as Appendix A is a Version With Markings to Show Changes Made.

The rejection of claims 1 and 21-24 under 35 U.S.C. 112 (1st para.) for lack of sufficient written description is respectfully traversed.

The U.S. Patent and Trademark Office has taken the position that "the issue is not simply the individual agents or stimuli disclosed in the specification but the operable combinations of them." It is also noted that the "specification provides no specific guidance on what combinations are most likely to be operable or what concentrations and degrees of stimulus exposure will most likely be operable." Applicants submit that the disclosure of the present invention is more than sufficient to demonstrate that they had possession of the claimed invention.

The "membrane-disrupting reagent" of the claimed invention is defined as a reagent that induces a membrane-denaturing reaction when the membrane is exposed to a stimulus, and includes, as described on page 9, lines 16-27, enzymes, antibody molecules, membrane bound proteins, glycoproteins, lipids, photosensitizers, oxidants, reductants, explosive compounds, magnetic particulates, metal particles, etc. In addition, the "stimulus" of the amended claims is restricted to those that induce the membrane-denaturing reaction of the membrane-disrupting reagent selected and includes electromagnetic waves, particle rays, heat, cooling, electricity, magnetism, oscillations, physical contact, chemical substances, cells, and viruses, as described on page 9, lines 6-15.

As set forth in the Declaration Under 37 C.F.R. § 1.132 by Katsuyoshi Ishii ("Ishii Declaration"), submitted with applicants' response to the first office action, the initial efficacy of a particular combination can be judged immediately after treatment using an injection marker, such as a water-soluble fluorescent dye (Ishii Declaration ¶ 7). Further, the long-term efficacy of a particular combination can be judged using a conventional cell detachment assay known in the art at the time of the present invention (Ishii Declaration ¶ 8). Using these techniques and routine experimentation, one of ordinary skill in the art would be readily able to select useful combinations of membrane-disrupting reagents and stimuli from those listed in the present application at suitable reagent concentrations and degrees of

stimulation (Ishii Declaration ¶¶ 6-8). Therefore, the rejection of claims 1 and 21-24 under 35 U.S.C. § 112 (1st para.) should be withdrawn.

Claim 21 recites the use of a specific combination of a reactive oxygen species as the membrane-disrupting reagent and either light energy, electrical energy, or chemical energy. Applicants believe that the claimed combination of a membrane-disrupting reagent and a stimulus fully satisfy the written description requirement, for the reasons noted above. In any event, at the very least, the more restricted combination of a membrane-disrupting reagent and a stimulus set forth in claim 21 would clearly meet this requirement, because these combinations are taught on page 12, lines 15-24 of the present application. Accordingly, the rejection of claim 21 under 35 U.S.C. § 112 (1st para.) should not be maintained.

The rejection of claims 1, 6, and 21-24 under 35 U.S.C. § 102(b) as anticipated by U.K. Patent Application Serial No. GB 2 209 468 A to Morgan ("Morgan") is respectfully traversed.

Morgan teaches a method of irradiating liposomes having an incorporated photosensitizing agent with light of the appropriate wavelength. This effects destabilization of the lipid bilayer and fusion between liposomes and/or exchange of membrane bound constituents of the liposomes between liposomes and/or cells or tissues of a recipient of the liposomes and/or fusion of intact liposomes with such cells or tissues. To read the claimed invention on Morgan, it is necessary to construe that reference's liposomes as both the support and membrane of the claimed invention. More particularly, the liposomes are the membranes being disrupted and are the supports holding the membrane-disrupting reagent. However, this possibility is foreclosed by the "membrane is separate and distinct from the support" limitation of claim 1. Support for this limitation is found, *inter alia*, in Figures 3, 4, 5, 6, and 7 of the present application. Since Morgan does not teach or in any way suggest this feature, it cannot be a proper basis for rejecting the claims.

In addition, Morgan is distinguishable from the present invention in that the method for introducing substances by membrane fusion technique as described in Morgan works only in liposomes, where the liposomes are made of the same material as the membrane to be disrupted. In contrast, the present invention relates to a membrane perforation technique, where the membrane to be disrupted is contacted with a membrane-disrupting reagent attached to a support and the support could be made of any material as

long as it facilitates precise contact of the membrane-disrupting reagent with the membrane. In other words, the material of the support is not limited to the same material as the membrane to be disrupted, as in Morgan, but could be made of anything including artificial material (e.g. microbeads).

Furthermore, the liposomes of Morgan are administered to a patient in a manner which permits them to freely move through blood vessels to, amongst other places, a target site. Localized treatment is then achieved by irradiating the free-moving liposomes which happen to be at the target site. By contrast, the membrane-disrupting reagent of the claimed invention does not freely move but "is attached to a support which facilitates precise contact of the membrane-disrupting reagent with the membrane". This achieves a controlled disruption of the membrane without permitting free movement of this reagent which can be wasteful and potentially detrimental to other sites of undesired contact. Since Morgan does not utilize a membrane-disrupting agent attached to a support, it does not form a proper basis to reject the claims of the present application.

Accordingly, for all the above reasons, the rejection based on Morgan is improper and should be withdrawn.

In view of all the foregoing, it is submitted that this case is in condition for allowance and such allowance is earnestly solicited.

Respectfully submitted,

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Nov. 11, 2002 — Ruth R. Smith

Date — Ruth R. Smith

Appendix A

Version With Markings to Show Changes Made

In reference to the amendments made herein to claim 1, additions appear as underlined text, while deletions appear as bracketed text, as indicated below:

In the claims:

Please amend claim 1 as follows:

1. (Twice Amended) A method of site specific regulated membrane disruption comprising:

contacting a membrane with a membrane-disrupting reagent that induces a membrane-denaturing reaction when the membrane is exposed to a stimulus, wherein the membrane-disrupting reagent is attached to a support which facilitates precise contact of the membrane-disrupting reagent with the [cell] membrane, wherein the membrane is separate and distinct from the support; and

applying the stimulus to the membrane at a contact site under conditions effective to temporarily and partially disrupt the membrane only at the contact site where permeability of the membrane recovers to the state prior to disruption.